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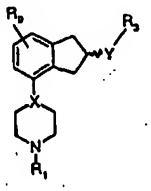
(54) Title: SUBSTITUTED INDAN DERIVATIVES

(57) Abstract

The present invention relates to new piperidyl- or piperazinyl-substituted indan derivatives having formula (I) wherein X is N or CH; Y is NR_2HC_2, CH_2NR_2, NR_2CO, $CONR_2$ or NR_2SO_2, wherein R_2 is H or C_1–C_6 alkyl; R_1 is H, C_1–C_6 alkyl or C_3–C_6 cycloalkyl; R_3 is C_1–C_6 alkyl, C_3–C_6 cycloalkyl or $(CH_2)_n$–aryl, wherein aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S which may be mono- or di-substituted; n is 0–4; R_9 is H, C_1–C_6 alkyl, C_3–C_6 cycloalkyl OCF_3, $OCHF_2$, OCH_2F, halogen, CN, CF_3, OH, C_1–C_6 alcoxy, C_1–C_6 alcoxy–C_1–C_6 alkyl, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C_1–C_6 alkyl; or COR_8, wherein R_6, R_7 and R_8 are as defined above, as *R*-enantiomers, *S*-enantiomers or racemates in the form of a free base or pharmaceutically acceptable salts or solvates thereof, a process for their preparation, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy.



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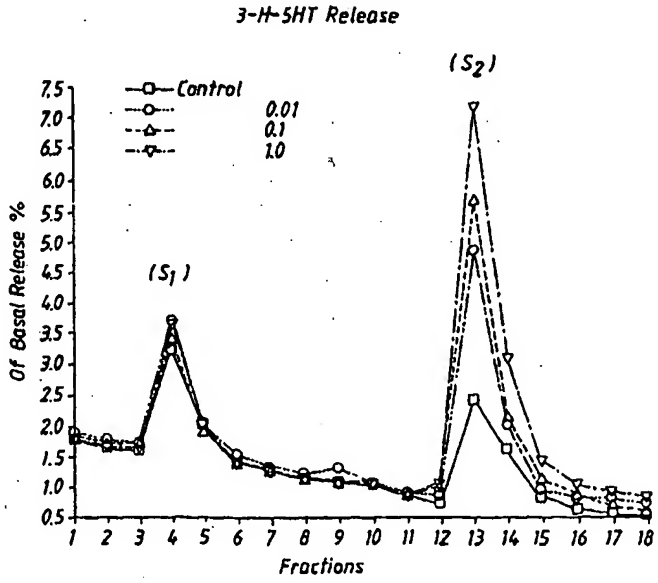

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SUBSTITUTED INDAN DERIVATIVES

Field of the Invention

The present invention relates to new piperidyl- or piperazinyl-substituted indan derivatives as *(R)*- enantiomers, *(S)*-enantiomers or racemates in the form of free base or pharmaceutically acceptable salts or solvates thereof, a process for their preparation, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy.

An object of the invention is to provide compounds for therapeutic use, especially compounds having a selective effect at a subgroup of 5-hydroxytryptamine receptors, designated the h5-HT_{1B}-receptor (previously called the 5-$HT_{1D\beta}$-receptor) in mammals including man.

It is also an object of the invention to provide compounds with a therapeutic effect after oral administration.

Background of the Invention

Various central nervous system disorders such as depression, anxiety, etc. appear to involve the disturbance of the neurotransmitters noradrenaline (NA) and 5-hydroxytryptamine (5-HT), the latter also known as serotonin. The drugs most frequently used in the treatment of depression are believed to act by improving the neurotransmission of either or both of these physiological agonists. It appears that the enhancement of 5-HT neurotransmission primarily affects the depressed mood and anxiety, whereas the enhancement of noradrenaline neurotransmission affects the retardation symptoms occurring in depressed patients. The invention concerns compounds which have an effect on 5-HT neurotransmission.

Serotonin, or 5-HT, activity is believed to be involved in many different types of psychiatric disorders. For instance it is believed that an increase in 5-HT activity is

associated with anxiety, while a decrease in 5-HT release is associated with depression. Serotonin has in addition been implicated in such diverse conditions as eating disorders, gastrointestinal disorders, cardiovascular regulation disorders and sexual disturbances.

The 5-HT Receptors

The various effects of 5-HT may be related to the fact that serotonergic neurons stimulate the secretion of several hormones, e.g. cortisol, prolactin, ß-endorphin, vasopressin and others. The secretion of each of these other hormones appears to be regulated on a specific basis by several different 5-HT (serotonin) receptor subtypes. With the aid of molecular biology techniques, to date these receptors have been classified as 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6 and 5-HT_7 with the 5-HT_1 receptor further divided into the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F} subtypes. Each receptor subtype is involved in a different serotonin function and has different properties.

Regulation of the 5-HT transmission

The release of 5-HT is feedback-regulated by two different subtypes of 5-HT receptors. Inhibitory 5-HT_{1A} autoreceptors are located on the cell bodies in the raphé nuclei which upon stimulation by 5-HT decrease the impulse propagation in the 5-HT neurons and thereby reducing the 5-HT released at the nerve terminals. Another subtype of inhibitory 5-HT receptors is located on the 5-HT nerve terminals, the $h5\text{-HT}_{1B}$ receptors (in rodents the $r5\text{-HT}_{1B}$ receptors) which regulate the synaptic concentration of 5-HT by controlling the amount of 5-HT that is released. An antagonist of these terminal autoreceptors thus increases the amount of 5-HT released by nerve impulses which has been shown in both *in vitro* and *in vivo* experiments.

The use of an antagonist of the terminal $h5\text{-HT}_{1B}$ autoreceptor will accordingly increase the synaptic 5-HT concentration and enhance the transmission in the 5-HT system. It would thus produce an antidepressant effect making it useful as a medication for depression.

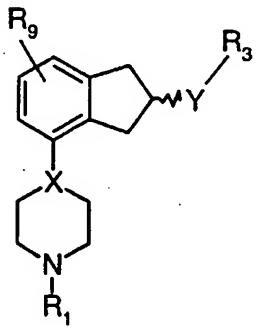
Other localizations of h5-HT_{1B} receptor subtype also exist. A large part of these postsynaptic receptors appear to be located on nerve terminals of other neuronal systems (so called heteroreceptors). Since the h5-HT_{1B} receptor mediates inhibitory responses an antagonist of this receptor subtype might also increase the release of other neurotransmitters than 5-HT.

Compounds having h5-HT_{1B} activity may according to well known and recognised pharmacological tests be divided into full agonists, partial agonists and antagonists.

Disclosure of the Invention

The object of the present invention is to provide compounds having a selective effect at the h5-HT_{1B} receptor, preferably antagonistic properties, as well as having a good bioavailability. The effect on the other receptors chosen from, for example, the 5-HT_{1A}, 5-HT_{2A}, D_1, D_{2A}, D_3, α_1 and α_2 receptor has been investigated.

Accordingly, the present invention provides compounds of the formula I



(I)

wherein

X is N or CH;

Y is NR_2CH_2, CH_2NR_2, NR_2CO, $CONR_2$ or NR_2SO_2

wherein R_2 is H or C_1-C_6 alkyl;

R_1 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or $(CH_2)_n$-aryl,

wherein aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or disubstituted with R_4 and/or R_5;

wherein R_4 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, NR_6R_7, OCF_3, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, phenyl, phenyl-C_1-C_6 alkyl, phenoxy, C_1-C_6 alkylphenyl, an optionally substituted heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 wherein the substituent(s) is(are) selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and phenyl-C_1-C_6 alkyl, an optionally substituted heteroaromatic ring containing one or two heteroatoms selected from N, O and S herein the substituent(s) is(are) selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and phenyl-C_1-C_6 alkyl, or COR_8;

wherein R_6 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_7 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

R_8 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, CF_3, NR_6R_7, phenyl, a heteroaromatic ring containing one or two heteroatoms selected from N, O and S or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2;

wherein R_5 is H, OH, CF_3, OCF_3, halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

n is 0-4;

R_9 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OCF_3, $OCHF_2$, OCH_2F, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, C_1-C_6 alkoxy- C_1-C_6 alkyl, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N, O and S wherein the substituent(s) is(are) C_1-C_6 alkyl; or COR_8; wherein R_6, R_7 and R_8 are as defined above,

as (*R*)-enantiomers, (*S*)-enantiomers or a racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof which possess a high selective effect at the h5-HT_{1B} receptor and also show sufficient bioavailability after oral administration.

In the present context C_1-C_6 alkyl may be straight or branched. C_1-C_6 alkyl may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl,i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl.

In the present context C_1-C_6 alkoxy may be straight or branched. C_1-C_6 alkoxy may be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy, i-pentyloxy, t-pentyloxy, neo-pentyloxy, n-hexyloxy or i-hexyloxy.

In the present context C_3-C_6 cycloalkyl may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

In the present context halogen may be fluoro, chloro, bromo or iodo.

In the present context the heteroaromatic ring containing one or two heteroatoms selected from N, O and S preferably is a 5- or 6-membered heteroaromatic ring and may be furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl or thienyl. The heteroaromatic ring can be either substituted or unsubstituted.

In the present context the heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 may optionally contain a carbonyl function and is preferably a 5-, 6- or 7-membered heterocyclic ring and may be imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, thiomorpholinyl, preferably piperidino, 1-piperazinyl, morpholino, thiomorpholino and 4-piperidon-1-yl.

A preferred embodiment of the invention relates to compounds of formula I wherein Y is NHCO or CONH i.e. amides. Of these compounds, the compounds wherein R_9 is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, $OCHF_2$ or OCH_2F and R_3 is unsubstituted phenyl, or mono- or di- substituted phenyl, and especially ortho-, meta- or para- substituted phenyl, and particularly these wherein the substituent R_4 is phenyl, phenyl-C_1-C_6 alkyl, cyclohexyl, piperidino, 1-piperazinyl, morpholino, CF_3, 4-piperidon-1-yl, n-butoxy or COR_8 wherein R_8 is phenyl, cyclohexyl, 4-piperidon-1-yl, 1-piperazinyl, morpholino, CF_3, piperidino or NR_6R_7, are preferred.

Examples of combinations of substituents are:

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 and R_9 are H;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 and R_9 are H;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 and R_9 are H;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_5 and R_9 are H;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_5 and R_9 are H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 and R_9 are H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is cyclohexyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 and R_9 are H;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7.

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 and R_9 are H;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 and R_9 are H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 and R_9 are H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 and R_9 are H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

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X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_9 is H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 and R_9 are H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 and R_9 are H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 and R_9 are H;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 and R_9 are H;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 and R_9 are H;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is morpholino, R_9 is H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is morpholino, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 and R_9 are H;

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X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is morpholino, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 and R_9 are H;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is COR_8, R_8 is NR_6R_7, $R_6R_7CH_3$, C_2H_5 or C_3H_7 and R_9 is H;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

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X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 and R_9 are H;

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X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

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X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is cyclohexyl, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is morpholino, R_9 is H;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_9 is H;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is COR_8, R_8 is NR_6R_7, $R_6R_7CH_3$, C_2H_5 or C_3H_7, R_9 is OCH_3;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

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X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is H;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

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X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is piperidino, R_5 is H, $R_9$is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 and R_9 are H;

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X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 and R_9 are H;

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X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is COR_8, R_8 is NR_6R_7, $R_6R_7CH_3$, C_2H_5 or C_3H_7, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 and R_9 are H;

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X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is cyclohexyl, R_9 is H;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

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X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

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X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

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X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is OCH_3;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is morpholino, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

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X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_4 is COR_8, R_8 is morpholino, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is morpholino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is piperidino, R_5 is H, R_9 is OCH_3;

X is N, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is morpholino, R_5 is H, R_9 is OCH_3;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is N, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is piperidino, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is $CONR_2$, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is $(CH_2)_2$-phenyl, R_9 is CH_3, C_2H_5 or C_3H_7;

X is CH, Y is NR_2CO, R_1 is H, CH_3, C_2H_5 or C_3H_7, R_2 is H, R_3 is CH_2-phenyl, R_4 is phenyl, phenylmethyl or phenylethyl, R_5 is H, R_9 is CH_3, C_2H_5 or C_3H_7.

A preferred compound is 4-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)-indan-2-carboxamide.

The compounds of the present invention are in the form of the racemate or the (*R*)- or (*S*)-enantiomer in the form of a free base or a pharmaceutically acceptable salt or solvate thereof. Compounds in the form of the (*R*)-enantiomer are believed to be preferred ones.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. Illustrative acids are sulfuric, nitric, phosphoric, oxalic, hydrochloric, formic, hydrobromic, citric, acetic, lactic, tartaric, dibenzoyltartaric, diacetyltartaric, palmoic, ethanedisulfonic, sulfamic, succinic, propionic, glycolic, malic, gluconic, pyruvic, phenylacetic, 4-aminobenzoic, anthranilic, salicylic, 4-aminosalicylic, 4-hydroxybenzoic, 3,4-dihydroxybenzoic, 3,5-dihydroxybenzoic, 3-hydroxy-2-naphthoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluenesulfonic, sulfanilic, naphthalenesulfonic, ascorbic, cyclohexylsulfamic, fumaric, maleic and benzoic acids. These salts are readily prepared by methods known in the art.

The preferred solvates of the compounds of this invention are the hydrates.

Pharmaceutical Formulations

In a second aspect the present invention provides a pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I as an enantiomer or a racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof, optionally in association with diluents, excipients or inert carriers.

According to the present invention the compound of the invention will normally be administered orally, rectally or by injection, in the form of pharmaceutical formulations comprising the active ingredient either as a free base or a pharmaceutically acceptable non-toxic acid addition salt, e.g. the hydrochloride, hydrobromide, lactate, acetate, phosphate, sulfate, sulfamate, citrate, tartrate, oxalate and the like, in a pharmaceutically acceptable dosage form. The dosage form may be a solid, semisolid or liquid preparation. Usually the active substance will constitute between 0.1 and 99% by weight of the preparation, more specifically between 0.5 and 20% by weight for preparations intended for injection and between 0.2 and 50% by weight for preparations suitable for oral administration.

To produce pharmaceutical formulations containing the compound of the invention in the form of dosage units for oral application, the selected compound may be mixed with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or poly-vinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a polymer known to the person skilled in the art, dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish

between tablets containing different active substances or different amounts of the active compound.

For the preparation of soft gelatine capsules, the active substance may be admixed with e.g. a vegetable oil or poly-ethylene glycol. Hard gelatine capsules may contain granules of the active substance using either the above mentioned excipients for tablets e.g. lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine. Also liquids or semisolids of the drug can be filled into hard gelatine capsules.

Dosage units for rectal application can be solutions or suspensions or can be prepared in the form of suppositories comprising the active substance in a mixture with a neutral fatty base, or gelatine rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil. Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing from about 0.1% to about 20% by weight of the active substance herein described, the balance being sugar and mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl-cellulose as a thickening agent or other excipients known to the person skilled in the art.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance, preferably in a concentration of from about 0.1% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

Suitable daily doses of the compound of the invention in therapeutical treatment of humans are about 0.01-100 mg/kg bodyweight at peroral administration and 0.001-100 mg/kg bodyweight at parenteral administration.

The compounds of the invention may be used in a combination with a 5-HT reuptake inhibitor, such as fluoxetine, paroxetine, citalopram, clomipramine, sertraline, alaproclate or fluvoxamin, preferably paroxetine or citalopram. Another possible combination is to use the compound of the invention together with a monoamine oxidase inhibitor, such as moclobemide, tranylcypramine, brofaromide or phenelzine, preferably moclobemide or phenelzine . Still another possible combination is the compound of the invention together with a 5-HT_{1A} antagonist, such as the compounds disclosed in WO 96/33710, preferably *(R)*-5-carbamoyl-3-(*N,N*-dicyclobutylamino)-8-fluoro-3,4-dihydro-2*H*-1-benzopyran.

Medical and Pharmaceutical Use

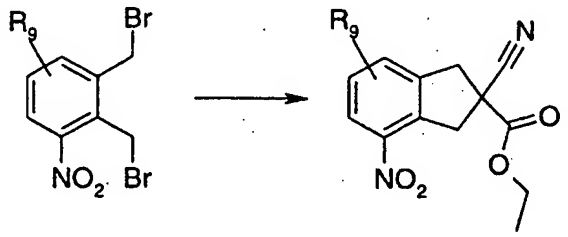
In a further aspect the present invention provides the use of the compounds of formula I in therapy as a h5-HT_{1B} antagonist, partial agonist or full agonist, preferably as an antagonist and the use in the treatment of 5-hydroxytryptamine mediated disorders. Examples of such disorders are disorders in the CNS such as mood disorders (depression, major depressive episodes, dysthymia, seasonal affective disorder, depressive phases of bipolar disorder), anxiety disorders (obsessive compulsive disorder, panic disorder with/without agoraphobia, social phobia, specific phobia, generalized anxiety disorder, posttraumatic stress disorder), personality disorders (disorders of impulse control, trichotellomania), obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders (age associated memory impairment, presenile and senile dementia), pathological aggression, schizophrenia, endocrine disorders (e g hyperprolactinaemia), stroke, dyskinesia, Parkinson´s disease, thermoregulation, pain and hypertension. Other examples of hydroxytryptamine mediated disorders are urinary incontinence, vasospasm and growth control of tumors (e g lung carcinoma).

Methods of Preparation

The present invention also relates to processes for preparing the compound of formula I. Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from,

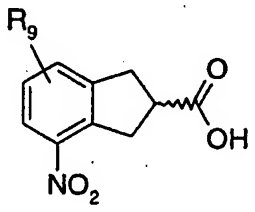
the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis" T.W. Greene, Wiley-Interscience, New York, 1991.

Methods of Preparation of Intermediates



(II) **(III)**

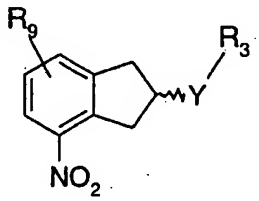
(i) Cyclization of the compound of formula **II**, where R_9 is hydrogen, to a compound of formula **III**, where R_9 is hydrogen, may be carried out in a suitable solvent such as *N,N*-dimethylformamide or dimethylsulfoxide in the presence of ethyl cyanoacetate and a suitable base such as K_2CO_3 or KOH. The reaction may occur between +20 °C and 100 °C.



(IV)

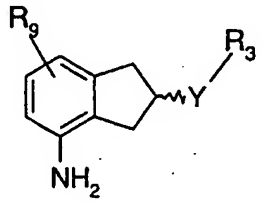
(ii) Conversion of a compound of formula **III**, where R_9 is hydrogen, to a compound of formula **IV**, where R_9 is hydrogen, may be carried by hydrolysis followed by decarboxylation under acidic conditions using acids such as HCl, HBr or H_2SO_4 in a suitable solvent such as acetic acid, water or mixtures thereof. The reaction may occur

between +20 °C and reflux. Hydrolysis under basic conditions may be carried out by using bases such as NaOH or KOH in a suitable solvent such as water, ethanol, methanol or mixtures thereof followed by decarboxylation under acidic conditions using acids such as HCl, HBr or H_2SO_4 in a suitable solvent such as acetic acid, water or mixtures thereof. The reaction may occur between +20 °C and reflux.



(V)

(iii) Conversion of a compound of formula **IV**, where R_9 is hydrogen, to a compound of formula **V**, where Y is $CONR_2$ and R_9 is hydrogen, may be carried out by activation of the acid function of a compound of formula **IV** as an acid halide such as an acid chloride with a suitable base such as a trialkylamine, e.g. triethylamine, or by using an activating reagent such as *N,N'*-carbonyldiimidazole, *N,N*-dicyclohexylcarbodiimide or diphenylphosphinic chloride with a suitable base such as *N*-methylmorpholine in a suitable solvent, e.g. methylene chloride, chloroform, toluene, *N,N*-dimethylformamide, dioxane or tetrahydrofuran, followed by the addition of an appropriate amine or aniline HNR_2R_3, where R_2 and R_3 are as in formula **I** above and the reaction may occur between 0 °C and +120 °C.



(VI)

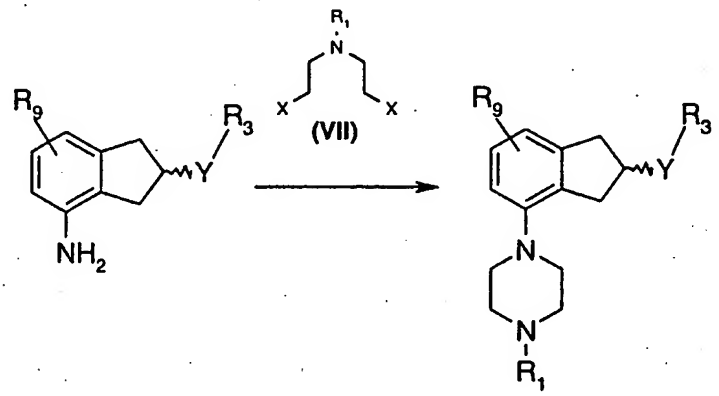
(iv) Conversion of a compound of formula **V** to a compound of formula **VI**, where Y is $CONR_2$, R_2 and R_3 are as in formula I above, may be carried out by hydrogenation using a

catalyst containing palladium, platina, nickel or rhodium in a suitable solvent such as ethanol, methanol or acetic acid at a reaction temperature between +20 °C and +120 °C; or by reduction with a suitable reductive reagent such as sodium dithionite in a suitable solvent such as *N,N*-dimethylformamide at a reaction temperature between +20 °C and +120 °C.

Methods of Preparation of End Products

Another object of the invention is a process for the preparation of the compound of general formula **I** by

reacting, in the case where Y is $CONR_2$; R_1, R_2, R_3 and R_9 are as defined in general formula **I** above, a compound of formula **A**



(A) **(I)**

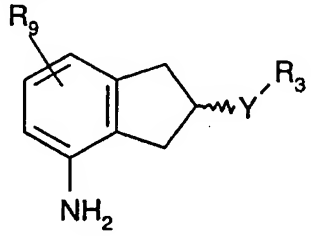
with a compound of formula **VII** wherein X is a leaving group.

Thus, the reaction according to the process **A** may be carried out with a compound of formula **VII** wherein X is a leaving group, e.g. a halogen such as chlorine or bromine or an alkane- or arenesulfonyloxy group such as p-toluenesulfonyloxy group. The process may be carried out in a suitable solvent such as ethanol, butanol, *N,N*-dimethylformamide,

acetonitrile or a mixture of water and acetonitrile with or without a suitable base, e.g. K_2CO_3, $NaHCO_3$ or KOH, and the reaction may occur between +20 °C and +150 °C.

Intermediates

Another object of the invention is a compound having the formula



wherein

Y is $CONR_2$ wherein R_2 is H or C_1-C_6 alkyl,

R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or $(CH_2)_n$-aryl,

wherein aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or di-substituted with R_4 and/or R_5; wherein R_4, R_5 and n are as defined above;

R_9 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OCF_3, $OCHF_2$, OCH_2F, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C_1-C_6 alkyl; or COR_8; wherein R_6, R_7 and R_8 are as defined above.

The invention is illustrated but not restricted to the following working examples.

Working Examples

Example 1

2-Cyano-2-ethoxycarbonyl-4-nitroindan.

A mixture of 2,3-di(bromomethyl)nitrobenzene (34 g, 0.11 mol; described in: EP 0529 636 A1), potassium carbonate (35 g, 0.25 mol) and ethyl cyanoacetate (12 mL, 0.11 mmol) in *N*,*N*-dimethylformamide (50 mL) was stirred at room temperature for 48 h. The solvent

was evaporated *in vacuo* and the residue was stirred with ethyl acetate. The mixture was filtered and the filtrate was washed with water and dried over sodium sulfate. The solvent was evaporated *in vacuo* to yield 29 g of the title compound as an oil (94% GC purity): EIMS (70 eV) *m/z* (relative intensity) 260 (4, M^+).

Example 2

4-Nitroindan-2-carboxylic acid.

A mixture of 2-cyano-2-ethoxycarbonyl-4-nitroindan (21 g, 81 mmol), acetic acid (290 mL), hydrochloric acid (37%, 130 mL) and water (140 mL) was stirred under reflux temperature over night. The acid was evaporated *in vacuo* and the residue was made alkaline with a 2 M sodium hydroxide solution. The mixture was stirred at room temperature, insoluble matter was filtered and the filtrate was acidified with hydrochloric acid. The obtained precipitate was filtered and washed with water to afford 18 gram of the crude acid: mp ~140 °C; EIMS (70 eV) *m/z* (relative intensity) 207 (40, M^+).

Example 3

4-Amino-*N*-(4-morpholinophenyl)indan-2-carboxamide.

A mixture of 4-nitroindan-2-carboxylic acid (2.2 g, 11 mmol), thionyl chloride (8.0 mL) and a catalytical amount of *N,N*-dimethylformamide in methylene chloride (20 mL) was stirred at reflux for 45 minutes. The solvent was evaporated *in vacuo* and the residue was dissolved in dry tetrahydrofuran and added, while stirring, to a mixture of 4-anilino-morpholine (1.7 g, 9 mmol) and potassium carbonate (3.0 g, 22 mmol) in acetonitrile (20 mL). The mixture was stirred for 1 h at 50 °C. After the addition of water (250 mL), the obtained precipitate was filtered, washed with water and dried to afford 2.9 g (78% yield) of crude 4-nitro-*N*-(4-morpholinophenyl)indan-2-carboxamide: EIMS (70 eV) *m/z* (relative intensity) 367 (100, M^+).

To a solution of the crude nitro compound (3.5 g) in *N,N*-dimethylformamide (25 mL) and water (3 mL) was added, in portions, sodium dithionite (7.0 g, 40 mmol). The mixture was stirred at 90 °C for 3 hours. The solvent was evaporated *in vacuo* and water (200 mL) was

added. The mixture was made alkaline with 2 M sodium hydroxide and extracted with chloroform. The phases were separated and the organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give 1.1 g of the crude product (GC purity 89%): EIMS (70 eV) *m/z* (relative intensity) 337 (100, M^+).

Example 4

4-(4-Methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)indan-2-carboxamide

A mixture of 4-amino-*N*-(4-morpholinophenyl)indan-2-carboxamide (1.1 g, 3 mmol), *N*-methyl-bis-(2-chloroethyl)amine hydrochloride (2.0 g, 10 mmol) and sodium hydrogen carbonate (8.0 g, 95 mmol) in 1-butanol (100 mL) was stirred over night at 120 °C. The mixture was filtered and the solvent was evaporated *in vacuo*. The crude residue (oil) was purified on a silica gel column using methylene chloride as the eluent to afford 100 mg of the title compound: mp 248-249 °C; EIMS (70 eV) *m/z* (relative intensity) 420 (47, M^+).

PHARMACOLOGY

Electrical field stimulation of [^{3}H] -5-HT release from occipital cortex of guinea pigs

[^{3}H]-5-HT is released by electrical field stimulation from slices of occipital cortex of guinea pigs which have been pre-incubated with [^{3}H]-5-HT. This release is similar to that caused by nerve stimulation, i.e. exocytotic release from serotonergic nerve terminals, depending on the presence of Ca^{2+} in the incubation medium. The 5-HT release is regulated at the level of the nerve terminals by autoreceptors, in the guinea pigs (like in humans) belonging to the h5-HT_{1B} receptor subtype. Thus, agonists of h5-HT_{1B} receptors reduce the amount of [^{3}H]-5-HT released by electrical field stimulation whereas the release is increased by antagonists of this receptor type. Testing compounds with this method is accordingly a convenient screening technique for determining the potency and functional effect of new h5-HT_{1B} receptor agonists and antagonists.

Methods and Materials

Buffer composition (mM) $NaHCO_3$ (25), NaH_2PO_4. H_2O (1.2), NaCl (117), KCl(6), $MgSO_4 \times 7H_2O$(1.2), $CaCl_2$(1.3), EDTA Na_2(0.03). The buffer is gassed for at least 30 min

before use. The pH of the buffer is about 7.2 at room temperature but it rises to about 7.4 at 37 °C.

Preparation of occipital cortical slices

Guinea pigs (200-250 g) were decapitated and the whole brain was removed. The occipital cortex was dissected and cut to slices 0.4x4 mm with McIlwain chopper machine. The white part of the tissue should be removed carefully with a tweezer before slicing. The slices were incubated in 5 ml buffer in the presence of 5 mM pargyline chloride. After incubation with 0.1 mM [^{3}H]-5-HT for another 30 min the slices were transferred to a test tube and washed three times with same volume buffer. The slices were transferred to the superfusion chambers with a plastic pipette and were washed for 40 min with the buffer in the presence of uptake inhibitor citalopram 2.5 µM with a flow 0.5 ml/min.

Electrical stimulation of 5-HT release

The superfused buffer was collected in 2 mL/fraction. The slices were stimulated by electricity with a train of pulses of frequency 3 Hz, duration 2 ms and current 30 mA for 3 min at the 4th and 13th fractions. The tested drugs were added from the 8th fraction to the end of experiment.

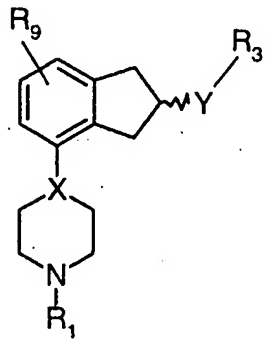
Results

A first electrical (or K^+) stimulation results in a standard amount of [^{3}H]-5-HT released (S_1). Before the first and the second stimulation the h5-HT_{1B} antagonist is added to the media which results in a dose depending increase of the release(S_2) after the second stimulation. See Fig.1.

The S_2/S_1 ratio which is the per cent of released [^{3}H]-5-HT at the second stimulation (S_2) divided by that of the first stimulation (S_1) was used to estimate drug effects on transmitter release.

CLAIMS

1. A compound having the formula **I**



(I)

wherein

X is N or CH;

Y is NR_2CH_2, CH_2NR_2, NR_2CO, $CONR_2$ or NR_2SO_2

wherein R_2 is H or C_1-C_6 alkyl;

R_1 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or $(CH_2)_n$-aryl,

wherein aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or di-substituted with R_4 and/or R_5;

wherein R_4 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, NR_6R_7, OCF_3, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, phenyl, phenyl-C_1-C_6 alkyl, phenoxy, C_1-C_6 alkylphenyl, an optionally substituted heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 wherein the substituent(s) is(are) selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and phenyl-C_1-C_6 alkyl, an optionally substituted heteroaromatic ring containing one or two heteroatoms selected from N, O and S wherein the substituent(s) is(are) selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and phenyl-C_1-C_6 alkyl, or COR_8;

wherein R_6 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_7 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

R_8 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, CF_3, NR_6R_7, phenyl, a heteroaromatic ring containing one or two heteroatoms selected from N, O and S or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2;

wherein R_5 is H, OH, CF_3, OCF_3, halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

n is 0-4;

R_9 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OCF_3, $OCHF_2$, OCH_2F, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N, O and S, wherein the substituent(s) is(are) C_1-C_6 alkyl; or COR_8; wherein R_6, R_7 and R_8 are as defined above,

as (*R*)-enantiomers, (*S*)-enantiomers or a racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 wherein Y is NR_2CO or $CONR_2$.

3. A compound according to any one of claims 1-2 wherein X is N.

4. A compound according to any one of claims 1-3 wherein R_1 is H or C_1-C_6 alkyl.

5. A compound according to any one of claims 1-4 wherein R_3 is $(CH_2)_n$-aryl.

6. A compound according to any one of claims 1-4 wherein R_3 is $(CH_2)_n$-aryl which is substituted with R_4, which is an optionally substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N, O and S, or COR_8.

7. A compound according to any one of claims 5 and 6 wherein n is 0.

8. A compound according to claim 6 wherein R_8 is NR_6R_7 or a heterocyclic ring containing two heteroatoms selected from N and O.

9. A compound according to any one of claims 1-8 wherein R_9 is H, C_1-C_6 alkyl, $OCHF_2$, halogen or C_1-C_6 alkoxy.

10. A compound according to any one of claims 1- 9 wherein X is N, Y is NR_2CO and R_9 is C_1-C_6 alkoxy.

11. A compound according to claim 10 wherein X is N, Y is NR_2CO, R_4 is morpholino or COR_8 and R_9 is C_1-C_6 alkoxy.

12. A compound according to any one of claims 1- 9 wherein X is N, Y is NR_2CO and R_9 is C_1-C_6 alkyl.

13. A compound according to claim 12 wherein X is N, Y is NR_2CO, R_4 is morpholino or COR_8 and R_9 is C_1-C_6 alkyl.

14. A compound according to any one of claims 1- 9 wherein X is N, Y is NR_2CO and R_9 is H.

15. A compound according to claim 14 wherein X is N, Y is NR_2CO, R_4 is morpholino or COR_8 and R_9 is H.

16. A compound which is 4-(4-methylpiperazin-1-yl)-*N*-(4-morpholinophenyl)indan-2-carboxamide in the form of a free base or a pharmaceutically acceptable salt or solvate thereof.

17. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1-16 as an enantiomer or racemate in the form of a free base or a pharmaceutically acceptable salt or solvate thereof optionally in association with diluents, excipients or inert carriers.

18. A pharmaceutical formulation according to claim 17 for use in the treatment of 5-hydroxytryptamine mediated disorders.

19. A pharmaceutical formulation according to any one of claims 17 or 18 for use in the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson´s disease, thermoregulatory disorders, pain, hypertension, urinary incontinence or vasospasm; or for growth control of tumors.

20. A compound as defined in any of claims 1-16 for use in therapy.

21 A compound as defined in claim 20 for use in the treatment of disorders in the central nervous system.

22. A compound as defined in claim 21 for use in the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson´s disease, thermoregulatory disorders, pain or hypertension.

23. A compound as defined in claim 22 for use in the treatment of urinary incontinence or vasospasm or for growth control of tumors.

24. A compound as defined in claim 20 for use in the treatment of 5-hydroxytryptamine mediated disorders.

25. A compound as defined in claim 24 for use as a h5-HT_{1B} antagonist.

26. The use of a compound defined in any of claims 1-16 in the manufacture of a medicament for the treatment of disorders in the central nervous system and/or urinary incontinence or vasospasm; or for growth control of tumors.

27. The use according to claim 26 in the manufacture of a medicament for the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson´s disease, thermoregulatory disorders, pain or hypertension.

28. The use of a compound defined in any of claims 1-16 in the manufacture of a medicament for the treatment of 5-hydroxytryptamine mediated disorders.

29. The use according to claim 28 wherein the compound according to any one of claims 1-16 is used as a h5-HT_{1B} antagonist.

30. A method for the treatment of disorders in the central nervous system and/or urinary incontinence or vasospasm or for growth control of tumors by administering to a mammal including man in need of such a treatment a therapeutically effective amount of a compound defined in any of claims 1-16.

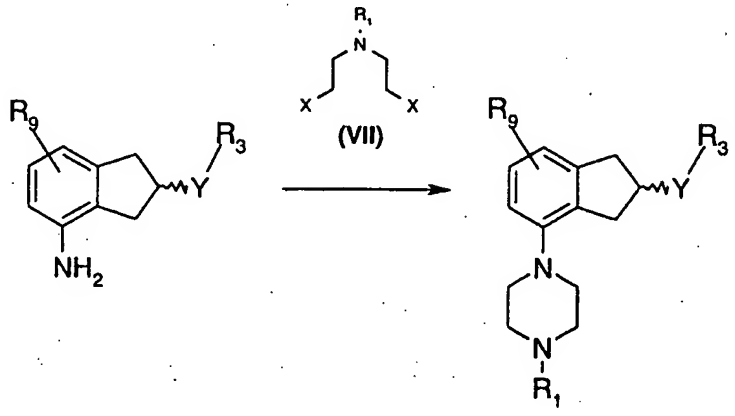
31. A method according to claim 30 for the treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual

disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson´s disease, thermoregulatory disorders, pain or hypertension.

32. A method for the treatment of 5-hydroxytryptamine mediated disorders by administering to a mammal including man in need of such a treatment a therapeutically effective amount of a compound defined in any of claims 1-16.

33 A method according to claim 32 wherein the compound according to any one of claims 1-16 is used as a h5-HT_{1B} antagonist.

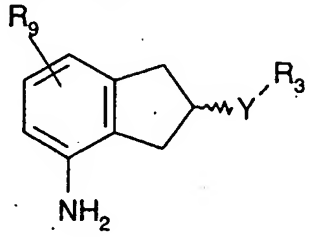
34. A process for the preparation of the compound of formula I according to claim 1 by reacting, in the case where Y is $CONR_2$, R_1, R_2, R_3 and R_9 is as defined in general formula I in claim 1, a compound of formula A



(A) (I)

with a compound of formula VII, wherein X is a leaving group.

35. A compound having the formula



wherein

Y is $CONR_2$ wherein R_2 is H or C_1-C_6 alkyl

R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or $(CH_2)_n$-aryl,

wherein aryl is phenyl or a heteroaromatic ring containing one or two heteroatoms selected from N, O and S and which may be mono- or di-substituted with R_4 and/or R_5;

wherein R_4 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, NR_6R_7, OCF_3, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, phenyl, phenyl-C_1-C_6 alkyl, phenoxy, C_1-C_6 alkylphenyl, an optionally substituted heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 wherein the substituent(s) is(are) selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and phenyl-C_1-C_6 alkyl, an optionally substituted heteroaromatic ring containing one or two heteroatoms selected from N, O and S wherein the substituent(s) is(are) selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and phenyl-C_1-C_6 alkyl, or COR_8;

wherein R_6 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R_7 is H, C_1-C_6 alkyl or C_3-C_6 cycloalkyl; and

R_8 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, CF_3, NR_6R_7, phenyl, a heteroaromatic ring containing one or two heteroatoms selected from N, O and S or a heterocyclic ring containing one or two heteroatoms selected from N, O, S, SO and SO_2 wherein R_6 and R_7 are as defined above;

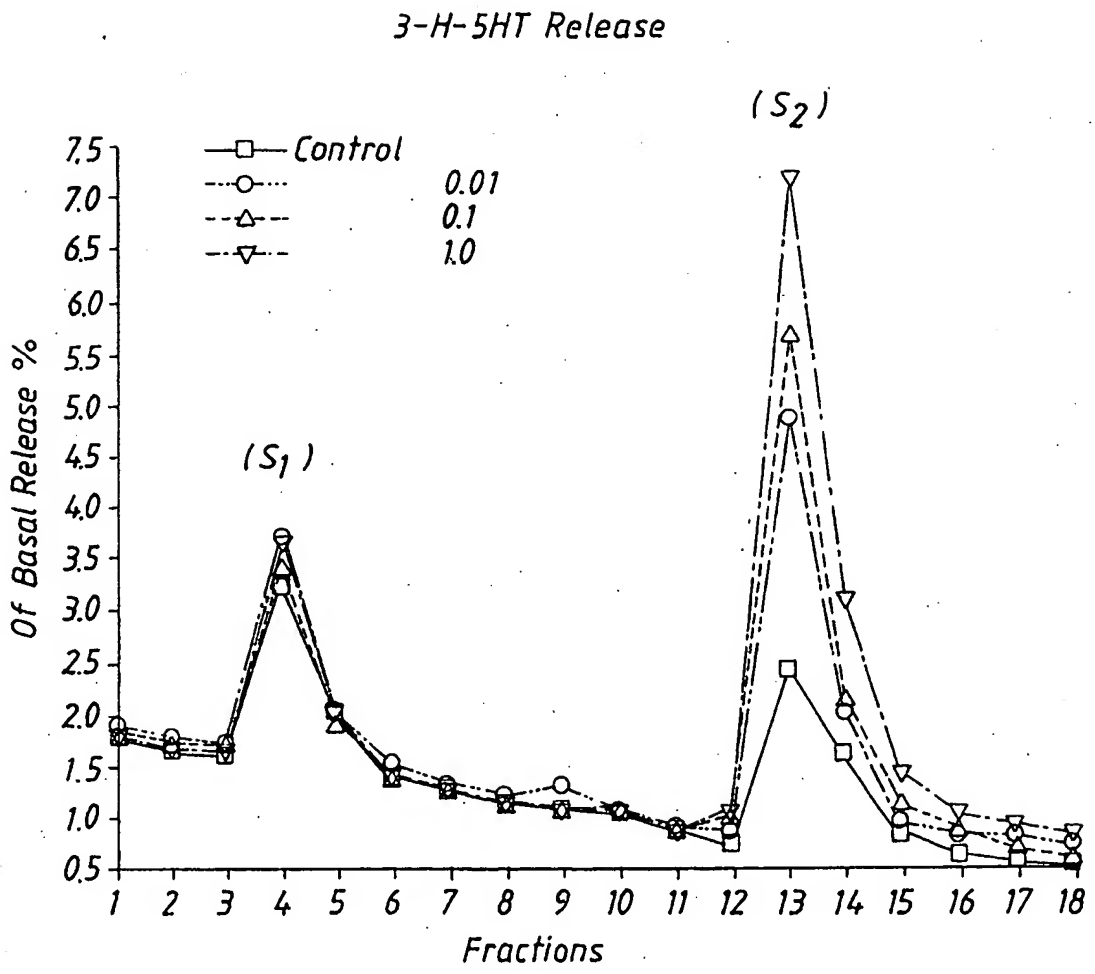
wherein R_5 is H, OH, CF_3, OCF_3, halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy;

n is 0-4;

and

R_9 is H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, OCF_3, $OCHF_2$, OCH_2F, halogen, CN, CF_3, OH, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, NR_6R_7, SO_3CH_3, SO_3CF_3, $SO_2NR_6R_7$, an unsubstituted or substituted heterocyclic or heteroaromatic ring containing one or two heteroatoms selected from N and O, wherein the substituent(s) is(are) C_1-C_6 alkyl; or COR_8; wherein R_6, R_7 and R_8 are as defined above.

Fig 1


3-H-5HT Release
(S2)
Control
0.01
0.1
1.0
(S1)
Of Basal Release %
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Fractions

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01605

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 295/135, C07D 295/155, C07D 211/26, C07D 211/34, A61K 31/495, A61K 31/445
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9734883 A1 (ASTRA AKTIEBOLAG), 25 Sept 1997 (25.09.97), the whole document --	1-29,34
X	WO 9421619 A1 (PFIZER INC.), 29 Sept 1994 (29.09.94), the claims -- --------	1-29

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 1999	20 -01- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01605

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 30-33
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/12/98

International application No.
PCT/SE 98/01605

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9734883 A1	25/09/97	AU 2186597 A	10/10/97
		AU 6949796 A	27/03/97
		HR 970166 A	30/04/98
		SE 9601110 D	00/00/00
WO 9421619 A1	29/09/94	AU 6391894 A	11/10/94
		CA 2158457 A	29/09/94
		EP 0689536 A	03/01/96
		FI 941213 A	17/09/94
		HU 67312 A	28/03/95
		HU 9400760 D	00/00/00
		IL 108923 D	00/00/00
		JP 2810236 B	15/10/98
		JP 8503228 T	09/04/96
		ZA 9401806 A	15/09/95